UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

HOFFMANN-LA ROCHE, INC and ROCHE MOLECULAR SYSTEMS, INC, Plaintiffs, v. PROMEGA CORPORATION, Defendant.	No. C-93-1748 VRW **ORDER**

The court tried the affirmative defense of defendant Promega Corporation against plaintiff Hoffman-La Roche in a 12-day trial commencing on February 1, 1999, and ending on February 22, 1999. Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law.

FINDINGS OF FACT

1. Promega Corporation (Promega) is a corporation headquartered in Madison, Wisconsin that produces for sale

reagents and other products for the life science community. Promega sells products in California and throughout the world.

2. Hoffmann-La Roche, Inc. is a New Jersey corporation operating in the state of California and throughout the world through subsidiaries and related companies, including Roche Molecular Systems, Inc. (together, Roche). Roche operates, inter alia, diagnostic pharmaceutical and life science research products businesses.

3. Roche filed this action against Promega alleging breach of a contract for the sale of Taq DNA Polymerase (Taq), infringement of certain patents and related causes of action. At issue here is United States Patent No. 4,889,818 (the '818 patent), entitled "Purified Thermostable Enzyme." The '818 patent, as well as the other patents in suit, were originally assigned to Cetus Corporation (Cetus) and were later sold to Roche. Promega denied the allegations of the complaint and alleged, as one of several affirmative defenses and counterclaims, that the '818 patent was obtained by inequitable conduct and therefore unenforceable.

4. The '818 Patent claims priority under 35 USC section 120 from Application No. 06/889,241 (the '241 application), filed on August 22, 1986. On June 17, 1987, Continuation-in-Part Application No. 07/063,509 (the '509

application) was filed and it resulted in issuance of the '818 Patent.

5. The '241 and '509 applications contain representations to the United States Patent and Trademark Office (PTO) made by the applicants in an attempt to have the application for a patent granted.

6. During the prosecution of the '241 application, the applicants submitted an information disclosure statement to the PTO identifying Alice Chien et al., Deoxyribonucleic Acid Polymerase from the Extreme Thermophile Thermus Aquaticus, 127 Journal of Bacteriology 3 (1976) and A. S. Kaledin et al., Isolation and Properties of DNA Polymerase From Extremely Thermophilic Bacterium Thermus Aquaticus YTI, 45 Biokhimiva 4 (1980) as material prior art.

7. The '241 and '509 applications were prepared in consultation with the inventors who provided the scientific information disclosed in the application.

8. The initial named inventors of the '241 and '509 applications were Dr. David Gelfand, Susanne Stoffel, Dr. Frances Lawyer and Randall Saiki. When these applications were filed, each of the named inventors filed declarations under penalty of perjury attesting that they had read the applications, that all statements in the applications were true

and that they understood their duty of disclosure arising from the duty of candor and good faith that they owed the PTO during prosecution of the patents.

9. On October 27, 1988, the PTO issued an office action rejecting the '509 application as anticipated under 35 USC section 102 and obvious under 35 USC section 103.

10. The office action also included a restriction requirement which required the applicants to elect to prosecute one of three groups of "distinct" inventions. Group I included claims 1-12 of the original '509 application; group II included claims 13-23 and group III included claims 24-30. Cetus patent attorney Kevin Kaster elected to prosecute group I.

11. On March 17, 1989, the inventors responded to the office action. The March 17, 1989, response to the office action contained representations made by the applicants designed to cause the patent examiner to withdraw her prior art rejections under 35 USC sections 102 and 103 in order to allow the '509 application to issue as a patent.

12. The March 17, 1989, response also canceled original claims 1 to 30 and added three new claims numbered 31 to 33. These became claims 1 to 3 in the '818 Patent.

13. An Information Disclosure Statement (IDS) was filed on March 7, 1989.

14. On or about March 7, 1989, Saiki and Lawyer were removed as named inventors of the '818 Patent. The accompanying petition was signed by Lawyer and Saiki on March 3, 1989.

15. The '818 Patent was issued on December 26, 1989, and has three claims. Those claims are as follows:

> 1. Purified thermostable Thermus aquaticus DNA polymerase that migrates on a denaturing polyacrylamide gel faster than phosphorylase B and more slowly than does bovine serum albumin and has an estimated molecular weight of 86,000-90,000 daltons when compared with a phosphorylase B standard assigned a molecular weight of 92,500 daltons.
>
> 2. The polymerase of claim 1 that is isolated from Thermus aquaticus.
>
> 3. The polymerase of claim 1 that is isolated from a recombinant organism transformed with a vector that codes for the expression of Thermus aquaticus DNA polymerase.

'818 Patent, Promega Exh 654 at col 44:45-58

16. In December 1991, Cetus assigned all of its right, title and interest in the '818 patent to plaintiffs Hoffman-La Roche and its wholly owned subsidiary Roche Molecular Systems, Inc.

17. Gelfand and Stoffel stated in sworn declarations to the PTO that they read the originally-filed '241 and '509

applications, indicating that they understood their duty of candor, had truthfully provided information to the PTO and had provided full and complete disclosure of all material information. Gelfand and Stoffel understood their obligations at the time of the patent applications, at the time of the office action response and at the time the IDS was prepared and filed.

18. Gelfand was aware of the office action and the response.

19. Gelfand provided information to patent attorney Kaster in order to respond to the office action and Kaster relied upon Gelfand in authoring that office action response.

20. Kaster also relied upon the ‘241 and ‘509 applications in providing a response to the PTO’s rejection.

21. With the exception of certain specific representations concerning the use of non-denatured gels in Chien et al., Gelfand reviewed the office action response before it was submitted to the PTO.

22. Gelfand is a knowledgeable scientist and fully understood the scientific concepts surrounding pH, fidelity, DNA, enzyme purification, molecular weight, nucleases, SDS-PAGE, gel filtration, sizing columns, phosphocellulose chromatography,

incorporation, specific activity and activity measurement, cloning, the polymerase chain reaction and other related scientific principles.

23. Gelfand was at the center of technical communications regarding Taq at Cetus, was aware of most data concerning Taq and was considered the primary source of information on Taq throughout the period 1986 to 1990. He was regularly consulted by individuals throughout the company on matters relating to Taq. Cetus relied upon Gelfand when making corporate decisions concerning Taq manufacturing, quality control, marketing, patent prosecution and scientific study.

24. As a routine matter, the attorneys in Cetus's patent department consulted on technical matters pertaining to patent applications with the inventors named on the patent.

25. At all times relevant to this action, Cetus had an ongoing partnership with Eastman Kodak designed in part to understand the characteristics of Taq.

26. In the October 27, 1988, office action rejecting the '509 application as anticipated by, or, in the alternative, obvious in light of Chien et al. and Kaledin et al., the examiner expressed concerns about the reliability of the molecular weight determinations reported in Chien et al. and Kaledin et al. She determined that she could not be certain

whether the difference in molecular weight between the claimed enzyme and the prior art was real or the product of different experimental parameters.

27. The applicants' March 17, 1989, response to the office action sought to persuade the examiner that the reported differences in molecular weight between the claimed enzyme and the enzymes isolated by Chien et al. and Kaledin et al. were not artifactual:

> Applicants believe that, at most, Chien et al. and Kaledin et al. isolated a crude preparation of degraded Taq polymerase. * * * Applicants believe that Chien et al. and Kaledin et al. at the very least, experienced a severe degradation problem in their purification process, and that such a problem kept those same researchers from discovering the present purified Taq polymerase.

March 17, 1989, Response to Office Action, Promega Exh 640 at 13.

28. In October 1986, before the applicants' response to the office action, Stoffel had experimental data indicating that a fragment of Taq, the so-called "Stoffel fragment," did not bind to phosphocellulose columns. Unlike Kaledin et al., who had used DNA cellulose columns, Chien et al. had used phosphocellulose columns in their chromatographic purification.

29. The results of Stoffel's experiment were never divulged to the examiner. Nor did Cetus or any of the inventors otherwise indicate to the PTO that they had information casting

doubt on the ability of fragments of Taq to bind to phosphocellulose columns.

30. The court previously found that Stoffel's experiment was material information that should have been disclosed to the examiner. See August 9, 1996, Order at 50-53. The court found that this information was material because Cetus's principal argument to distinguish Chien et al. was that Chien et al. had isolated a degraded form of Taq. Stoffel's data tends to undermine this argument because it suggests that degraded forms of Taq would have been lost earlier in the chromatography process and would not have been recovered by Chien et al. Similarly, all data in the inventors' possession suggesting that Taq does not bind, or binds only weakly, to phosphocellulose columns was material.

31. Stoffel testified that she did not appreciate the significance of this experiment for the argument made to the PTO regarding the molecular weight of the enzyme isolated by Chien et al. She testified that it did not occur to her to bring the results of the experiment to anyone's attention. This testimony is not credible in that Stoffel and the other inventors at Cetus had discovered that the prior art had not generated a proteolytic fragment.

32. Gelfand became aware of Stoffel's results that under certain conditions, Taq fragments would not bind to

phosphocellulose columns. Gelfand reflected his knowledge of this in numerous communications with outside contractors who produced Taq for Cetus.

33. Roche argues that Gelfand believed only that Taq fragments would bind to phosphocellulose columns under the salt conditions used by Chien et al. As the court found in its August 9, 1996, order, however, this could only mean that Gelfand was uncertain as to the implications of the binding properties of Taq fragments for analysis of the difference between the enzyme isolated by Chien et al. and the claimed enzyme. See August 9, 1996, Order at 52.

34. In light of their scientific backgrounds, experience in the purification of enzymes and participation in the prosecution of the '818 patent, neither Stoffel or Gelfand could have failed to appreciate the significance of the information in their possession.

35. The parties' respective experts provided diametrically opposing views on whether the failure of Gelfand and Stoffel to disclose this information evidenced an intent to deceive the PTO. Dr. Michael Chamberlin testified that because of the difference in salt conditions between Stoffel's experiment and Chien et al.'s experiment, nothing about Stoffel's experiment would lead a reasonable scientist to believe that Chien et al. could not have isolated a Taq

fragment. Dr. Dale Mossbaugh testified that the failure of Stoffel and Gelfand to disclose the information in their possession suggesting that Taq fragments do not bind to phosphocellulose columns rendered the statements in the applicants' March 17, 1989, response to the office action misleading and would constitute scientific misconduct in an academic setting.

36. Gelfand and Stoffel could have replicated the experiments conducted by Chien et al. and Kaledin et al. and compared the resulting enzyme with the enzyme of the '818 patent. Such side-by-side comparison of the enzymes would be the best way to determine whether the inventors had, in fact, isolated a new enzyme. Gelfand's testimony to the contrary is not credible. Such side-by-side experimentation was never performed.

37. The Taq fragment information known to the inventors cast sufficient doubt on their representations to the PTO regarding the results obtained by Chien et al. to trigger a duty either to report that information to the PTO or replicate the prior art in order to rebut the negative implications of that information. The inventors intentionally concealed the data in their possession indicating that Taq does not bind, or binds only weakly, to phosphocellulose columns.

38. The inventors stated in the March 17, 1989, response to the office action that: "The present inventors discovered that a problem existed with the Chien et al. and Kaledin et al. procedures: the procedures did not yield full-length Taq polymerase."

39. By stating that they "discovered" something about the prior art, the inventors did not implicitly claim to have replicated the prior art. Evidence adduced by the inventors led them to believe that the prior art had generated something other than that which the inventors purified.

40. The applicants did not fail to disclose a western blot performed by Lawyer which demonstrated that Kaledin et al had isolated full-length Taq polymerase.

41. Lawyer analyzed the results of an experiment conducted by Stoffel. The record does not establish that the Stoffel experiment Lawyer analyzed was a replication of Kaledin et al. Rather, it appears that the Stoffel experiment was "a slight modification" of the Kaledin et al procedure, which is consistent with the applicants' representations to the PTO. See id.

42. Accordingly, the court finds that the Lawyer experiment was not material and that failure to disclose it was not misleading.

43. The applicants made representations in the March 17, 1989, response to the office action concerning the relative level of template dependence exhibited by the enzymes isolated by Chien et al and Kaledin et al as compared to the enzyme of the '818 patent. Specifically, the applicants observed that Kaledin et al reported that in the absence of any one deoxynucleoside triphosphate, the enzyme Kaledin et al isolated incorporated only 20 to 29 percent as much nucleotide triphosphate as when all four deoxynucleoside triphosphates were present. The applicants observed that Chien et al reported that their enzyme incorporated only 21 to 39 percent as much nucleotide triphosphate in the absence of any one deoxynucleoside triphosphate as in the presence of all four. The applicants concluded from these results that the enzymes isolated by Chien et al and Kaledin et al "are not suitable for template-directed in vitro DNA synthesis, because the enzymes have a rather substantial promiscuous ability to synthesize DNA on a natural DNA template in the absence of one of the four deoxynucleoside triphosphates." March 17, 1989, Response to Office Action, Promega Exh 640 at 16. The degree of template dependence of the Chien et al and Kaledin et al enzymes was contrasted with the enzyme of the '818 patent: "the purified Taq polymerase of the invention has little or no activity on a DNA polymerase assay reaction mixture that does not contain one of the four deoxynucleoside triphosphates." Id.

44. The '818 patent itself contains representations regarding the template dependence of the enzyme claimed therein:

> Finally, when one or more nucleotide triphosphates were eliminated from a DNA polymerase assay reaction mixture, very little, if any, activity was observed using the enzyme herein, and the activity was consistent with the expected value, and with an enzyme exhibiting high fidelity. In contrast, the activity observed using the Kaledin et al. (supra) enzyme is not consistent with the expected value, and suggests misincorporation of nucleotide triphosphates(s).

'818 Patent, Promega Exh 654 at col 30:23-31.

45. Based on the representations contained in the March 17, 1989, response to the office action and the '818 patent itself, the court finds that the inventors effectively represented to the PTO that the enzyme of the '818 patent exhibited greater template-dependence than the enzymes isolated by Chien et al. and Kaledin et al. and lower misincorporation (or higher fidelity) than the enzyme isolated by Kaledin et al.

46. The testimony of patent attorney Kaster, the principal author of the March 17, 1989, response, establishes the materiality of those representations. Kaster testified that although the principal argument advanced in favor of the patentability of the '818 enzyme was based on molecular weight, he included representations regarding template-dependence and fidelity because he believed that if the patent examiner was unpersuaded that the '818 enzyme was patentable based on

molecular weight, she might nevertheless allow the patent to issue with limitations directed to template dependence and/or fidelity.

47. Having reviewed the office action response, the inventors were aware of this line of argument and therefore of the materiality of representations concerning fidelity and incorporation.

48. Promega's expert, Dr. Thomas Kunkel, testified that the applicants' representations regarding the relative template dependence of the '818 enzyme and the Kaledin et al. and Chien et al. enzymes were false. According to Kunkel, the experiments upon which the applicants based their claim that the '818 enzyme exhibited little or no activity in the absence of one of the four deoxynucleoside triphosphates utilized a different substrate than did Chien et al. or Kaledin et al. Kunkel testified that the reported differences in the activity of the '818 enzyme and the Chien et al. and Kaledin et al. enzymes in the absence of a deoxynucleoside triphosphate was due almost entirely to differences in the substrate used, not to differences in the properties of the enzymes.

49. Kunkel also testified that the representation in the '818 patent, at column 30 lines 23-31, that the Kaledin et al. enzyme has higher misincorporation than the '818 enzyme is erroneous. According to Kunkel, Kaledin et al. did not perform

any “fidelity experiment” that would allow the inventors to reach any conclusions regarding the rate of misincorporation exhibited by the Kaledin et al. enzyme. Kunkel also testified that the experiments conducted by the inventors on the ‘818 enzyme also did not relate to incorporation. Accordingly, Kunkel concluded that the representations made to the PTO that the Kaledin et al. enzyme exhibited greater misincorporation than does the ‘818 enzyme were unjustified and erroneous.

50. Kunkel testified that Gelfand’s knowledge of the scientific principles of fidelity, template-dependence and incorporation was such that Gelfand could not have unintentionally made the errors described above. Kunkel’s testimony demonstrated that he had an adequate basis for his opinion of Gelfand’s knowledge regarding fidelity, template-dependence and incorporation:

(1) Kunkel reviewed an abstract of an article co-authored by Gelfand in 1980 that demonstrated knowledge of the differences between substrates;

(2) Kunkel reviewed an experiment conducted by Gelfand and Stoffel in 1980 related to the purification of an enzyme called terminal transferase which demonstrated their knowledge of the principles of template dependence;

(3) Kunkel testified that he had numerous conversations with Gelfand during the time period in question on

these subjects and gave a seminar at Cetus regarding these principles at which Gelfand was present;

(4) Gelfand was present at a conference at which Kunkel gave a presentation relating to this subject matter at the Banbury Conference Center in New York in 1988;

(5) Gelfand was present at another conference in Keystone, Colorado a few months after the Banbury conference at which Kunkel gave another presentation relating to this subject matter;

(6) Kunkel discussed with Gelfand, and Gelfand subsequently cited, an article written by Tindall & Kunkel on the incorporation properties of a very similar, if not identical, enzyme.

51. The Tindall & Kunkel article served as a basis for collaboration between the authors and Gelfand's own group at Cetus.

52. Based on his understanding of Gelfand's level of expertise regarding principles of fidelity, template dependence and incorporation, Kunkel testified that the representations made to the PTO regarding the template dependence and incorporation properties of the '818 enzyme vis-a-vis the enzymes isolated by the prior art were intentionally misleading. Kunkel testified that these representations would constitute academic misconduct and that, in relation to these representations, Gelfand was a "scientific fraud."

53. Roche did not introduce any expert testimony regarding fidelity, template dependance or incorporation. Kunkel's testimony was essentially unrebutted.

54. The court finds that Kunkel was a credible, well-credentialed and knowledgeable witness.

55. Based in part on Kunkel's testimony and in light of all other evidence, the court finds that the representations described at ¶¶ 43-44 were erroneous and made with the intent to mislead the PTO.

56. Example VI of the '818 patent states: "Active fractions with no detectible nuclease(s) were pooled and run on a silver stained SDS PAGE mini gel. The results show a single -88 kd band with a specific activity of -250,000 units/mg." '818 Patent, Promega Exh 654, col 41:14-16.

57. The court has previously concluded that the -250,000 units/mg figure is erroneous and that "given the importance Cetus placed on this figure as an indication of the superior purity of their Taq polymerase, and given the importance which Cetus placed on this superior purity argument as an argument for the patentability of their Taq polymerase, the court concludes that this was a material misstatement." August 9, 1996, Order at 58, 55-58.

58. Having participated in the prosecution of the '818 patent, the inventors were aware of the emphasis placed on purity and therefore were aware of the materiality of representations concerning purity.

59. Gelfand and Stoffel never actually performed Example VI of the '818 patent as written.

60. The court finds that the inventors' failure to perform the example in the patent that supposedly yielded the erroneous -250,000 units/mg figure is persuasive evidence of their intent to deceive the PTO. The inventors simply could not have believed that the -250,000 units/mg figure was correct and accurate given that they never performed the experiment that they represented to the PTO had yielded that figure.

61. An internal Cetus memorandum dated October 4, 1988, that was copied to Gelfand states:

> Is the specific activity up to 260,000 units per mg a specification guarantee that we can support? NO, it is research data on one batch not yet submitted for publication, the assay is difficult to carry out on each lot. Best to say 'value from Cetus corporation' or cite 'personal communication, D. Gelfand, Cetus Corp.' and use the value of 'around 200,000 units/mg in the salmon sperm assay.' * * * Gelfand's title of BTFH [Bio-Tech Folk Hero] will sway the doubters, I am sure.

October 4, 1988, Memorandum from J. Raymond, Promega Exh 189 at 1. As noted above, Gelfand was the primary source of information about Taq at Cetus and the primary researcher on the

Taq project and was copied on the memorandum. The court finds that information regarding specific activity contained in the Raymond memorandum came from Gelfand.

62. Gelfand was aware of the information contained in the memorandum. It therefore appears that Gelfand was willing to approve inclusion of a -250,000 units/mg specific activity figure in the '818 patent even though a very similar figure was not considered reliable enough to provide to customers and the figure that was considered reliable enough to provide to customers was considerably lower than -250,000 units/mg.

63. Gelfand gave conflicting testimony concerning the source of the specific activity value of -250,000 units/mg reported at column 41, lines 14-16 of the '818 patent. In his declaration submitted to the court on December 21, 1995, Gelfand reported that this figure was determined using the method taught in Example VI of the patent at column 30, lines 14-34. See December 21, 1995, Declaration of David H. Gelfand, Promega Exh 216 at 17:1-6. In a prior declaration submitted to the PTO, Gelfand stated that this figure was determined based on the method taught in Example I of the patent, at column 30, lines 3-16. See November 2, 1992, Declaration of David H. Gelfand, Promega Exh 95 at 3. Gelfand subsequently admitted that Example VI of the patent had never been done. Rather, it appears that the specific activity value reported a column 41 was derived by

extrapolating from experiments done partially in accordance with Example VI.

64. The court finds that the inventors intended to mislead the PTO by including the -250,000 units/mg figure for specific activity in Example VI, or were, at a minimum, reckless.

65. Example VI itself was a misrepresentation to the PTO. Because it was written in the past tense, Example VI communicated to the PTO that the experiment described therein had actually been performed and the results reported therein had actually been obtained by performing the experiment as written.

66. The applicants represented that the results showed a single -88 kd band with specific activity of -250,000. The entire preceding example, including the immediately preceding phrase--"[a]ctive fractions with no detectable nuclease(s) were pooled and run on a silver stained SDS PAGE mini gel"--was written in the past tense. Example VI included a great deal of experimental detail and nothing therein indicated that it should be interpreted as a prophetic example. The court therefore finds that Example VI communicated to the PTO that the experiment had actually been performed as written and that the results reported had actually been achieved by the method described in Example VI.

67. Example VI was never performed as written and thus did not yield the figures reported to the PTO. See supra ¶ 62.

68. Example VI reported measurements of Taq's purity and specific activity. See '818 patent, Promega Exh 654 at col 41:10-20. The applicants argued that the '818 enzyme was distinct over the prior art on the basis of each of these properties and the results reported in Example VI supported these arguments. Accordingly, the court concludes that it would have been important to a reasonable examiner to know that Example VI had never been performed as written and the results reported therein never achieved by the procedures as written.

69. Gelfand understood that when experiments are described using the past tense, the author represents that the procedures described have actually been performed as written and the results reported have actually been achieved using those procedures. Stoffel also understood that a scientist using the past tense represents that the experiment described has actually been performed. The inventors were aware of the materiality of reporting Example VI in the past tense, without indicating that it was prophetic.

71. Although the inventors may have believed that Example VI was superior to either of the two purification methods on which it was based, the court finds that Example VI was written in the past tense in order to deceive the PTO into

believing that it had actually been performed. The fact that Example VI may have been a superior method of purification is irrelevant: it had not been performed as written, the inventors knew that it had not been performed as written and they understood the significance of using the past tense to describe experiments. Under these circumstances, the court finds that the inventors' misrepresentation was intentional.

72. The applicants claimed that the specific activity of Taq produced by the method taught in Example VI of the '818 patent "is more than an order of magnitude higher than that claimed for the previously isolated Taq polymerase and is at least an order of magnitude higher than for E coli polymerase 1." '818 Patent, Promega Exh 654 at col 41:17-20. The applicants also stated that "the purified enzyme preparation of the invention has a specific activity more than ten times higher than the preparations described in the prior art." March 17, 1989, Response to Office Action, Promega Exh 640 at 17.

73. The assay conditions under which the inventors measured the specific activity of the claimed enzyme differs from the conditions under which Kaledin et al. and Chien et al. measured the specific activity of their enzymes.

74. Mossbaugh provided credible testimony that changes in the conditions under which an enzyme is assayed will affect the specific activity measurement. Accordingly, in order

meaningfully to compare the specific activity of the claimed enzyme and the prior art enzymes, the enzymes would have to be assayed under the same conditions. Any other comparison is improper.

75. Chamberlin testified that although changes in assay conditions do affect specific activity measurements, the differences between the assay conditions used by the inventors and those used by the prior art were not significant enough to account for more than a 20 percent difference in specific activity. Chamberlain's estimate was not based on any experimental work, but was "speculation" based on his review of the assay conditions.

76. Chamberlin's reasoning appears to be based, at least in part, on the difference observed when measuring the specific activity of Thermus Aquaticus crude cell extract under the assay conditions used by the inventors and the prior art. Reliance on the specific activity measurements of crude cell extracts appears to contradict one of the basic tenets of enzymology.

77. The court finds that Chamberlin's testimony that the differences in assay conditions would generate only a 20 percent difference in the specific activity value was not credible.

78. The court finds that making comparisons between the specific activity of the '818 enzyme and the prior art enzymes without first assaying the '818 and prior art enzymes under the same conditions was deceptive and resulted in an improper comparison of specific activity values.

79. The court has previously found that representations concerning specific activity are material and that the inventors knew that such representations were material. See August 9, 1996, Order at 58, 55-58.

80. The inventors understood that different assay conditions would produce different specific activity measurements. Accordingly, the inventors knew that the comparisons made in the '818 patent were deceptive and improper.

81. The court therefore finds that these comparisons were made with the intent to deceive the PTO or were, at a minimum, reckless.

82. The following specific statements were made concerning the molecular weight of the prior art and the molecular weight of the '818 invention:

> The molecular weight of the purified enzyme is reported as 62,000 daltons per monomeric unit.
>
> ***
>
> The pooled material from the column is dialyzed and analyzed by gel filtration to have a molecular weight of about 63,000

> daltons, and, by sucrose gradient centrifugation of about 68,000 daltons.

‘818 Patent, Promega Exh 654 at col 1:44-46, 55-59.

83. In the office action rejecting the ‘509 application, the examiner expressed doubts about whether the claimed differences in molecular weight between the ‘818 enzyme and the prior art were real or artifactual.

84. The applicants therefore devoted a great deal of attention and emphasis to molecular weight determinations in their response to the office action. In particular, they argued that the molecular weight determinations of the prior art were accurate and that the “simplest way to distinguish the present enzyme from the enzyme described by Chien et al. and Kaledin et al. is by molecular weight.” March 17, 1989, Response to Office Action, Promega Exhibit 640 at 11.

85. The inventors were in possession of four sources of information indicating that molecular weight measurements of Taq made by sizing column techniques would tend to understate the weight of Taq: (1) a memorandum by Jonathan Raymond; (2) data generated by Dr. Robert Drummond; (3) information that Taq is hydrophobic and (4) the results of an ultragel experiment conducted by Stoffel. These sources indicate that Taq polymerase tends to interact with several matrices used in size exclusion chromatography and consequently elutes later than

would be expected. When this occurs, the molecular weight measurement understates the true weight of the enzyme.

86. A memorandum by Raymond stated:

> The mw of Taq DNA Polymerase is 94 kDa, based on the amino acid sequence. On SDS gels the mw calculated is 94 kDa using assumptions about certain high mw standard proteins. It migrates differently on [Z]orbax or other sizing columns as if it binds even in high salt so need SDS to get good mw determination.

September 22, 1988, Memorandum from J. Raymond, Promega Exh 130 at 4. Promega's expert, Dr. Richard Burgess, confirmed the significance of this information for computing the molecular weight of Taq.

87. Although Gelfand admits having seen the memorandum, his testimony does not make clear when he saw it. As noted above, however, Gelfand was the primary source of information about Taq at Cetus and the primary decisionmaker on the Taq project. Gelfand was also copied on the memorandum. The court therefore finds that Gelfand received the memorandum and was aware of the information contained therein at the time the memorandum was written.

88. Test data generated by Drummond indicated that a significantly lower molecular weight measurement of Taq polymerase could result from the use of sizing columns.

89. Gelfand knew of Drummond's data.

90. Gelfand also knew that the preparation of Taq that Drummond tested was very impure. Gelfand therefore considered any results from those tests irrelevant.

91. Gelfand was aware at the time of the filing of the office action response that Taq was hydrophobic. Saiki's notebook states: "David Gelfand's experience with this polymerase indicates that it is a sticky enzyme and that he routinely uses both detergents during purification to improve yield and during assay to stimulate activity." Saiki Notebook No 2369, Promega Exh 665 at 101; Tr 458:22-459:2.

92. Burgess testified that knowledge of Taq's hydrophobicity confirms and helps explain its tendency to bind to sizing columns, thereby generating artifactually low molecular weight measurements by size exclusion chromatography. A scientist with Gelfand's background and training would have understood this.

93. Stoffel performed an experiment using an ultragel matrix that suggests that Taq interacts with that matrix. Gelfand was aware of this experiment.

94. Stoffel's ultragel experiment for molecular weight determinations using size exclusion chromatography "suggests

that there is an interaction with the resin and the only time that gel filtration columns are a valid measure of molecular weight is if there is no interaction with the resin." Tr 840.

95. Based on the Raymond memorandum, the Drummond data, the Stoffel ultragel experiment and the knowledge of Taq's hydrophobicity, the inventors had substantial information in their possession to indicate that molecular weight measurements of Taq using size exclusion chromatography might produce artifactually low results.

96. The inventors never disclosed the Raymond memorandum, Drummond data, Stoffel ultragel experiment or knowledge of Taq's hydrophobicity to the PTO. Nor did the inventors otherwise communicate to the PTO that they had information indicating that molecular weight determinations using size exclusion chromatography might produce artifactually low results.

97. The court previously found that the September 22, 1988, Raymond memorandum was material information that should have been disclosed to the PTO. See August 9, 1996, Order at 49-50. Because the inventors sought primarily to distinguish the claimed enzyme from the prior art based on molecular weight and because the patent examiner expressed doubts about the reliability of the molecular weight determinations of the prior art, the court concluded that "information relating to the

actual molecular weight of the prior art enzymes is 'material' in this case." Id at 50. Accordingly, the Drummond data, Stoffel's ultragel experiments and knowledge of Taq's hydrophobicity were also material and should have been disclosed to the PTO.

98. The inventors knew, based on their scientific knowledge and involvement in the prosecution of the '818 patent, that information bearing on the reliability of the prior art's molecular weight measurements was material.

99. As noted above, the inventors could have replicated the experiments conducted by Chien et al. and Kaledin et al. and compared the resulting enzyme with the claimed enzyme. This would have been the most reliable method for determining whether they had, in fact, isolated a new enzyme. Such side-by-side experimentation was never done.

100. The inventors' failure to replicate the prior art is persuasive evidence that their failure to disclose the information in their possession suggesting that Taq binds to sizing columns was intended to deceive the PTO. The inventors were in possession of information that undermined arguments made to the PTO to distinguish prior art. Had a side-by-side comparison revealed that a different enzyme was isolated by the prior art, the negative implication of this information for the inventors' arguments would have been rebutted. The inventors,

however, did not perform such experiments. Instead they simply concealed this information from the PTO.

101. Gelfand understood that if Taq interacts with the matrix during size exclusion chromatography, then the molecular weights reported by Chien et al. using that method would be artifactually low.

102. A scientist of Gelfand's knowledge and background would have known, based upon the information reviewed above, that the information provided to the PTO was incomplete and incorrect.

103. The inventors' failure to disclose information in their possession which suggested that Taq binds to sizing columns was a material misrepresentation made with the intent to deceive the PTO.

104. As part of Example VI of the patent, the inventors represented that: "Active fractions with no detectable nuclease(s) were pooled and run on a silver stained SDS PAGE mini gel. The results show a single -88 kd band with a specific activity of -250,000 units/mg." '818 Patent, Promega Exh 654, col 41:12-16.

105. As noted above, Example VI of the patent was never performed as written. Rather, Gelfand and Stoffel

combined steps from purifications numbered three and four to arrive at Example VI, which they considered the best method for purifying Taq.

106. The representation that Example VI yielded a single -88 kd band on an SDS PAGE mini-gel was necessarily a misstatement because the inventors had not, in fact, performed Example VI of the patent. Gelfand and Stoffel both conceded at trial that they never achieved a single band by performing Example VI as written.

107. Cetus argued to the patent examiner that even if the claimed enzyme was identical to the prior art enzymes, "[a]pplicants would still be entitled to a patent because the present preparations are far more pure than the Chien et al. and Kaledin et al. preparations." March 17, 1989, Response to Office Action, Promega Exh 640 at 17. The court has previously held that "[s]ince Cetus argued that the patent could issue based on the asserted purity limitation, a reasonable examiner would have considered important information which indicated that Cetus had overstated the level of purity of the claimed enzyme." August 9, 1996, Order at 58 n18. A reasonable examiner would therefore have considered important the fact that the inventors had never achieved "a single -88 kd band." That misrepresentation was therefore material.

108. Having participated in the patent prosecution, the inventors were aware that representations regarding purity were material.

109. Preparation 3, one of the two purification protocols that the inventors testified they used to arrive at Example VI, did not yield a single band on an SDS PAGE mini-gel. Roche's own expert Chamberlin testified to that effect.

110. Preparation 4, the other of the two purification protocols that the inventors testified they used to arrive at Example VI, very nearly yielded a single band. Stoffel testified that she achieved a single band using preparation 4. Gelfand conceded that more than one band appeared from preparation 4. Chamberlin stated that the SDS PAGE results for preparation 4 showed a predominant single band, as well as faint bands that in his experience did not reflect the presence of other proteins.

111. The inventors were also aware that United States Biochemical (USB) and Molecular Biology Resources (MBR), Cetus's outside Taq contractors, had not achieved single-band purity using the Example VI protocol.

112. The fact that Example VI was not performed is persuasive evidence the inventors intended to mislead the PTO when they stated that they had achieved a single -88 kd band on

an SDS PAGE mini-gel. The inventors simply could not have believed that they achieved a single -88 kd band given that they never performed the experiment that they represented to the PTO had yielded that figure.

113. The evidence in their possession reflects that only once, using a method similar but not identical to Example VI, were the inventors able to purify Taq to very nearly obtain a single band. The contrary evidence regarding the ability of Example VI to achieve a single band was much more abundant.

114. Moreover, preparation 4 was not the same as Example VI. Even if the inventors believed that Example VI could only yield a more pure result, they were not entitled to assume that this would happen: They were under a duty either to confirm that Example VI in fact yielded a single band, or else disclose to the PTO that their belief that Example VI would yield a single band was just that.

115. The inventors did not represent any specific level of purity to their customers, even years after making the single-band representation to the PTO. The court infers that this reflected the inventors' knowledge that they had deceived the PTO.

116. Mossbaugh provided credible testimony that the inventors knew the representation regarding the presence of a

single band as a result of the Example VI protocol was incorrect at the time it was made.

117. The court finds that the inventors' material misrepresentation that they achieved a single -88 kd band on an SDS PAGE mini-gel was made with the intent to deceive the PTO. It was, at a minimum, reckless.

118. The applicants made certain representations to the PTO concerning the differences in pH profile of the '818 enzyme in contrast to the prior art enzyme, as follows:

> Also, the enzymes herein have a broader pH profile than that of the thermostable enzyme from Thermus aquaticus described in the literature, with more than 50% of the activity at pH 7 as at pH 8.

'818 Patent, Promega Exh 654 at col 2:47-52.

> The results [of the '818 Example I preparation] showed that at pH 6.4 the polymerase was more than one-half as active as at pH 8.0. In contrast, Kaledin et al. found that at pH about 7.0, the enzyme therein had 8% of the activity at pH 8.3. Therefore, the pH profile for the thermostable enzyme herein is broader than that for the Kaledin et al. enzyme.

Id at col 30:17-22.

In explaining the rejection of the '509 application, the examiner wrote:

> Applicants further claim a broader pH range of activity for the instant enzyme. Variables known to effect pH range include reaction temperature, reaction buffer etc. It is not clear whether or not the molecular weight and pH range of activity claimed by applicants for the instant enzyme is a result

> of experimental parameters or an enzyme activity different than that previously described in the literature.

October 27, 1988, Office Action, Promega Exh 601 at 6.

Responding to the examiner's comments the applicants stated:

> Applicant [sic] have set forth in the specification many different examples of how the present enzyme patentably differs from the crude preparations of Chien et al. and Kaledin et al. Some of the most easily grasped differences include the differences in molecular weight and activity. With respect to activity, Applicants have demonstrated not only difference in the activity vs. pH profile but also a difference in specific activity between the present and prior art enzymes.

Response to Office Action, Promega Exh 640 at 11.

> On that same page of the application [47], at lines 1-5, Applicants also point out that the pH vs. activity profile of the present enzyme is very different from the profiles reported for the Chien et al. and Kaledin et al. enzymes. Examiner suggested that such differences were merely the result of different laboratory techniques. Applicants believe the foregoing should convince Examiner that Chien et al. and Kaledin et al. isolated an enzyme with distinctly different properties as compared to the claimed Taq polymerase of the invention. Because Chien et al. and Kaledin et al. isolated a different enzyme than did the present inventors, Applicants believe the anticipation/obviousness rejection based on the Chien et al. and Kaledin et al. references should be withdrawn.

Id at 16-17.

119. The representation that the '818 enzyme "was more than one-half as active" at pH 6.4 as at pH 8.0 was not

supportable. No such information existed at the time the statement was made in the notebooks or other experiments of the inventors. Stoffel testified that inclusion of this statement was unintentional and may have been a misprint.

120. Promega did not clearly and convincingly prove that this error was made with the intent to deceive the PTO.

121. The data shown in the patent was not accurately compared to the data in Kaledin et al. because the temperature corrections for the pH data of both the patent and the Kaledin et al. reference were not specified. Further, the Kaledin et al. reference did not specify whether the pH data reported therein had been corrected for temperature.

122. Stoffel testified that the failure to include a temperature correction for the '818 enzyme pH values was an oversight.

123. Although Kaledin et al. do not expressly indicate whether their data was temperature corrected, their citation to Chien et al., who did provide temperature corrected data, shows that Kaledin et al. were aware that their data needed to be corrected for temperature. See A. S. Kaledin et al., Isolation and Properties of DNA Polymerase From Extremely Thermophilic Bacterium Thermus Aquaticus YTI, 45 Biokhimiva 4 (1980), Promega Exh 112 at H008684 n4. Also, it was generally known that such

data needed to be corrected for temperature. Accordingly, the inventors had reason to believe that Kaledin et al.'s data was temperature corrected and therefore comparable to the pH profile of the '818 enzyme.

124. Promega did not clearly and convincingly prove that the inventors intended to deceive the PTO by failing to provide temperature corrections for the pH values given for the '818 enzyme or by making a pH profile comparison with Kaledin et al.

125. The distinction between the pH profiles of the Chien et al. enzyme and the '818 enzyme stated in the office action response had no factual basis. Arnold testified that plotting the pH data from the specifications of the '818 patent on Chien et al.'s Figure 3, which represented the PH profile of the enzyme Chien et al. isolated, shows that there is no basis for a reasonable scientist to argue that there is any difference in the pH profiles of the Chien et al. and '818 enzymes.

126. Stoffel testified that she could distinguish the '818 enzyme from the Chien et al. enzyme based on pH profiles using the pH profile shown at Figure 3 of Chien et al. Stoffel's testimony contradicted her statements at her deposition, although she attributed this difference to having been provided with an illegible copy of the Chien et al. reference at her deposition. Stoffel never explained, however,

how she could distinguish the pH profiles of the respective enzymes, nor did Roche introduce any other evidence rebutting Arnold's analysis. Accordingly, the court concludes that Stoffel's statement that she could distinguish the Chien et al. and '818 enzymes based on pH profile is entitled to little weight.

127. Promega has not proved clearly and convincingly, however, that any flawed comparison made between the Chien et al. and '818 enzymes' pH profiles was made with the intent to deceive the PTO. Evidence that Gelfand and Stoffel were knowledgeable about the principles of pH measurement does not suffice.

128. Dr. J.W.H. Sutherland prepared a report, prior to the office action response, that demonstrated that the pH profile of Kaledin et al. was very similar to the pH Profile of the '818 enzyme. See A.R. Mack & J.W.H. Sutherland, Technical Report: Dependence of Rate Upon PH of Reaction Buffer, Promega Exh 240; Tr 322-24, 323-29.

129. Promega did not prove clearly and convincingly, however, that any of the inventors ever read or learned the content of Sutherland's report. Accordingly, the court cannot find that any misrepresentation regarding this report was made with the intent to deceive the PTO.

130. The patent applicants made certain representations to the PTO concerning freedom from nuclease activity as follows:

> The fractions determined to have no deoxyribonuclease activity are pooled and dialyzed against the same buffer used in the third step.

'818 Patent, Promega Exh 654 col 6:42-44.

> The pooled fractions having thermostable polymerase activity and no deoxyribonuclease activity are dialyzed against a buffer at pH 8.0.

Id at col 6:49-52.

> Only those DNA polymerase fractions (65-95 mM potassium phosphate) having minimal nuclease contamination were pooled.

Id, Example I at col 29:46-48.

> Fractions with no significant endonuclease or double-strand exonuclease when assayed at 55° C. with 5 polymerase units were pooled and designated Fraction VII.

Id, Example VI at col 40:50-53.

> Active fractions with no detectable nuclease(s) were pooled and run on a silver stained SDSPAGE mini gel.

Id, Example VI at col 41:12-14.

> The Taq polymerase purified as described above in Example VI was found to be free of any contaminating Taq endonuclease and exonuclease activities.

Id, Example VII at col 41:23-25.

131. As to Example VI of the patent, the representations that "[a]ctive fractions with no detectable nuclease(s) were pooled and run on a silver stained SDS PAGE

mini-gel" and that "[t]he Taq polymerase purified as described above in Example VI was found to be free of any contaminating Taq endonuclease and exonuclease activities" were necessarily false because, as noted above, Example VI of the patent was never performed as written.

132. As noted, Cetus argued to the patent examiner that even if the claimed enzyme was identical to the prior art enzymes, "[a]pplicants would still be entitled to a patent because the present preparations are <u>far more pure</u> than the Chien et al. and Kaledin et al. preparations." March 17, 1989, Response to Office Action, Promega Exh 640 at 17. The court has previously held that "[s]ince Cetus argued that the patent could issue based on the asserted purity limitation, a reasonable examiner would have considered important information which indicated that Cetus had overstated the level of purity of the claimed enzyme." August 9, 1996, Order at 58 n18. A reasonable examiner would therefore have considered important the fact that the inventors had never achieved a preparation of Taq polymerase free from nuclease contamination.

133. Having participated in the patent prosecution, the inventors were aware that representations and information regarding purity were material.

134. The inventors asserted at trial that preparation 4 was the closest approximation to Example VI that they had

actually performed. The inventors relied on Example VI to support their argument that they had achieved a nuclease free preparation of Taq polymerase.

135. Stoffel conceded that preparation 4 was not nuclease free, although she argued that it contained only "a very small amount, minimal amount, of nuclease." Tr 1063. Most persuasive, however, was the testimony of Roche's own expert Chamberlin:

> Q. Let's cut to the chase. It's not free of nucleases, is it, sir?
> A. It's not what?
> Q. Free.
> A. It's not totally free, no.
> Q. So you are not representing to the court somehow that prep 4 satisfies the statements in the patent that the preparation prepared according to example 6 was free of nucleases, are you, sir?
> A. No.

Tr 2292-93.

136. The fact that Example VI was never performed is persuasive evidence that the inventors intended to mislead the PTO when they stated that they had achieved a nuclease-free preparation of Taq. The inventors simply could not have believed that they achieved a nuclease-free preparation of Taq given that they never performed the experiment that they represented to the PTO had yielded that result.

137. There was no evidence presented at trial that the inventors achieved a nuclease-free preparation of Taq polymerase

by any method at the time they made the above-referenced representations to the PTO.

138. The inventors were also aware that USB and MBR, Cetus's outside Taq contractors, had not achieved nuclease-free preparations of Taq polymerase. The protocols provided to the contractors were nearly identical to Example VI, although some lots were less faithful reproductions than others. Nevertheless, the fact that the inventors had these results in their possession at the time that they made the representations concerning nuclease-free preparations of Taq to the PTO is evidence that they intended to deceive the PTO.

139. The inventors' deceptive intent is also evident in Cetus's unwillingness to represent any specific level of purity to its customers, even years after making the nuclease-free representations to the PTO. Dr. Stuart Linn provided credible testimony that a scientist of Gelfand's background could not have made the statements made concerning a nuclease free preparation without knowing that they were false.

140. The court finds that the inventors' material misrepresentation that they achieved a nuclease-free preparation of Taq polymerase was made with the intent to deceive the PTO.

141. In her initial rejection of the '509 application, the examiner expressed concerns about the reliability of molecular weight measurements based on SDS PAGE:

> It is know [sic] that some proteins behave anomalously when subjected to SDS page, particularly very basic or acidic proteins etc. * * * It is not clear whether or not the molecular weight an [sic] pH range of activity claimed by applicants for the instant enzyme is a result of experimental parameters or an enzyme activity different than the [sic] previously described in the literature.

October 27, 1988, Office Action, Promega Exh 601 at 6.

In response, the following statements were made to the PTO:

> [T]he prior art references relied on by Examiner to reject the claims report molecular weights much lower than 86,000-90,000 for the DNA polymerases described in the references. In both of these references, [Kaledin and Chien et al.] the authors show polyacrylamide gels, both denaturing and non-denaturing, that demostate [sic] that the DNA polymerase described in the references migrates at approximately the same rate as bovine serum albumin (BSA). Because BSA has a molecular weight of 66.2 kd, and because the prior art references do describe the behavior of the DNA polymerase on polyacrylamide gels, Examiner cannot reasonably maintin [sic] that merely anomalous gel behavior explains the significant differences between the present invention and the prior art. The new claims now exclude a DNA polymerase that migrates in the same molecular weight range as BSA from the claimed subject matter. Thus, the present claims now clearly and concisely distinguish the claimed invention over the prior art.

March 17, 1989, Response to Office Action, Promega Exh 640 at 6.

> Applicants also respectfully direct Examiner's attention to Figure 1 of Chien et

> al., the associated legend, and the text at page 1551 of Chien et al., which together show that the Chien et al. Thermus aquaticus DNA polymerase migrates at the same rate as does bovine serum albumin (molecular weight of -66kd) during non-denaturing gel electrophoresis.

Id at 13.

142. The court previously addressed these statements and concluded that these statements erroneously informed the PTO that Chien et al. used denaturing PAGE analysis to determine the molecular weight of their enzyme. See August 9, 1996, Order at 47-48. The court noted that "[Roche] admit[s] that Cetus made these representations to the PTO and admit[s] that they were erroneous; in fact Chien et al. used only non-denaturing PAGE analysis, and did not use these results to estimate molecular weight." Id at 48.

143. The court also concluded that the applicants were directly responding to

> the examiner's concern that the difference in molecular weights between the '818 and prior art enzymes was caused by anomalous behavior during PAGE by asserting that the prior art had used PAGE itself and, therefore, any anomalies introduced by PAGE would have been constant across the prior art and Cetus's result. Given this argument by Cetus, a reasonable patent examiner certainly would have found the information that Chien et al. did not use PAGE for measuring molecular weight to be material * * * .

Id at 48.

144. Kaster, the Cetus attorney who drafted the March 17, 1989, office action response, acknowledged that the representation at page 13 of the response that Chien et al. had shown that their enzyme migrated at the same rate as bovine serum albumin using non-denaturing PAGE was erroneous. He attributed the error to using an unclear copy of the Chien et al. reference while drafting that portion of the response, which led him incorrectly to identify which of several bands in tube B of figure 4 corresponded to the polymerase Chien et al. were testing.

145. Kaster also testified, with respect to the representation at page 6 of the response, that when he stated that "the authors show polyacrylamide gels, both denaturing and non-denaturing," he did not mean to suggest that both authors--Kaledin et al. and Chien et al.--had used both types of gels, but that both types of gels were used by one or the other of the two authors. Thus, while he may not have written clearly, Kaster argues that he did not intend by that statement to suggest that Chien et al. used denaturing PAGE.

146. The examiner could easily have determined that Chien et al. used nondenaturing, but not denaturing, PAGE by examining the Chien et al. paper itself.

147. Promega has not proved clearly and convincingly that either Kaster or the inventors intended to deceive the

examiner by stating or implying that Chien et al. used non-denaturing PAGE, or by claiming that Chien et al. had shown that their enzyme migrated at the same rate as bovine serum albumin.

148. Claim three of the '818 patent is directed to: "The polymerase of claim 1 that is isolated from a recombinant organism transformed with a vector that codes for the expression of Thermus aquaticus DNA polymerase." '818 Patent, Promega Exh 654 at col 44:55-58.

149. Example V of the patent provided the inventors' best mode for producing rTaq. Example V describes a method whereby commercially available insert fragments are subcloned into two plasmids, which are in turn cut and assembled to form the Taq gene. See '818 Patent, Promega Exh 654 at col 37:34-38:61.

150. It is undisputed that the inventors never performed Example V as written in the patent.

151. Because Example V contained the best mode with respect to one of the three claims in the patent, a reasonable examiner would have considered it important to know that it had never been performed in determining whether to allow the application to issue as a patent.

152. The testimony of Dr. O'Farrell, Roche's expert, was that the method actually used by the inventors to construct the Taq gene was probably inferior to the method described at Example V. O'Farrell testified that Example V represented the conventional approach in the field at the time and that he would have chosen that method over the method actually used by the inventors. Promega introduced no rebutting testimony on this point.

153. Promega's expert Roberts testified that the method taught in Example V did not enable the invention. He argued that although the Example V method does allow one skilled in the art to assemble the gene, it does not provide sufficient information to allow one skilled in the art to confirm without undue experimentation that he or she has successfully assembled the correct gene. Roberts argued that the problems confirming the gene stemmed from errors in the restriction map.

154. Roberts was unwilling to conclude based on the evidence he reviewed that the errors in the restriction map were intentional. He could not rule out careless error.

155. O'Farrell testified that it was common in the art at the time for restriction maps to contain errors and that those skilled in the art knew to expect such errors.

156. O'Farrell also testified that one skilled in the art could assemble the gene by the method taught in Example V and confirm that the correct gene had been assembled without undue experimentation. O'Farrell's testimony was that the confirmation could take as little as a few days or as long as a few months depending on the approach the investigator utilized to confirm that he or she had conducted the experiment correctly. Roberts testified, by contrast, that it could take one skilled in the art between a few months and a year to assemble and confirm the gene. Roberts conceded at trial that he initially believed that Example V provided a workable method for constructing the Taq gene, but argued that he changed his mind upon further reflection.

157. In light of the directly conflicting testimony of O'Farrell, the court cannot conclude that Roberts' testimony provides clear and convincing evidence that the method taught in Example V requires one skilled in the art to engage in undue experimentation in order to confirm the proper assembly of the gene.

158. Promega also argues that the fact that Gelfand had sequence data available to him for the Taq gene demonstrates that the restriction map errors were intentionally left uncorrected. The experts agreed that sequencing information enables a scientist of Gelfand's background to produce a correct restriction map.

159. Gelfand had only partial sequence data.

160. O'Farrell testified that the restriction map included in the '818 patent was drawn based on a "puzzle solving method" for determining the restriction sites. O'Farrell testified that without the full sequence, a reasonable scientist might decide not to correct the restriction map using only partial sequence data, because the restriction map should be based entirely on the same type of data, not on a combination of "puzzle-solving" and sequence data.

161. None of the inventors was ever asked why the restriction map was not corrected in light of the sequencing data.

162. The court cannot conclude that Promega has proved clearly and convincingly that the inventors intentionally provided an erroneous restriction map in order to deceive the PTO about the best mode for producing recombinant Taq.

163. Promega also asserts that the inventors failed to disclose that they had expressed rTaq using E Coli bacteria containing the expression vector pLSGI. The experts agreed that "cloned enzymes" such as the one used by the inventors were known at the time to be the best mode for producing enzymes.

164. The inventors first produced rTaq using E Coli on June 10, 1987, only a week before the continuing-in-part application leading to the '818 patent was filed on June 17, 1987. O'Farrell provided credible testimony that a reasonable scientist would have conducted more experiments after first producing rTaq using E Coli before concluding that this provided the best mode for producing rTaq. Roberts' testimony largely confirmed that the experimentation described by O'Farrell as necessary to determine whether the E Coli method was the best mode was not done as of June 17, 1987. Roberts did not establish that it was not necessary to conduct these experiments before indicating the E Coli method as the best mode.

165. Promega's own expert Roberts testified from his own experience filing patents that he did not believe that there was any requirement that an inventor claiming a protein disclose the genetic sequence in the patent or deposit a clone containing the full-length gene. This militates against a finding that the inventors sought to deceive the PTO by not disclosing the sequence or depositing a clone containing the full-length gene. Nor does the court find that the misrepresentation that Example V was performed as written in the patent was made intentionally to deceive the PTO.

166. The court cannot find that the inventors' subjective belief at the time the continuing-in-part application was filed was that using E Coli containing plasmid pLSGI was the

best mode for producing rTaq. Accordingly, failure to disclose this method was not inequitable conduct, nor is it evidence that the misrepresentation that Example V was performed as written was made with the intent to deceive the PTO.

167. The court finds that the failure to perform Example V, although a material misrepresentation, was not made with the intent to deceive the PTO.

168. The March 17, 1989, Information Disclosure Statement filed by Cetus states:

> Applicants believe NEB [New England Biolabs] began promoting the release of Taq polymerase sometime in April, 1987. However, in October, 1987, catalog update, cited on the attached P.T.O. 1449 form, NEB still was announcing the forthcoming availability of Taq polymerase. Applicants believe NEB's delayed introduction of Taq polymerase resulted from their failure to discover Applicant's novel compositions and purification protocols.

Information Disclosure Statement, Promega Exh 616 at 11.

169. Promega asserts that the reference to Taq production by New England Biolabs (NEB) was misleading because (1) the Information Disclosure Statement fails to note that the NEB Taq was produced by a modification of the method taught in Chien et al. and (2) the inventors were aware that NEB had begun marketing full-length Taq polymerase in early 1987.

170. The '818 patent application claimed priority from the '241 application filed on August 22, 1986. Accordingly, the NEB enzyme was not prior art.

171. The failure to mention that the NEB Taq was derived by a modification of the method taught in Chien et al. did not render the March 17, 1989, Information Disclosure Statement misleading. The record does not establish that the inventors were aware of how NEB had modified the Chien et al. protocol. Absent that information, the mere fact that NEB indicated that it used a modification of Chien et al. to produce full-length Taq was not evidence that Chien et al. had themselves produced full-length Taq.

172. Promega never demonstrated that NEB's October 1987 catalogue update did not, in fact, announce the forthcoming availability of Taq as the inventors represented to the PTO. Accordingly, Promega never demonstrated the literal falsity of that representation.

173. Moreover, although Gelfand testified that Cetus purchased a lot of full-length Taq polymerase from NEB in July 1987, he also testified that Cetus experienced storage problems with that polymerase. The record establishes that NEB's enzyme had storage problems in early 1987 that cast doubt on the commercial viability of the NEB Taq polymerase.

174. Accordingly, the court finds that the statements made regarding NEB polymerase were not misleading, material or made with the intent to deceive the PTO.

175. The response to the office action cites work conducted on Thermus aquaticus done in the laboratory of Dr. Trela as follows:

> To make Examiner's reconsideration and withdrawal of the rejection easier, Applicants direct Examiner's attention to the attached abstract presented at the 1988 American Society of Microbiology Annual Meeting (#K47, p.214). The research described by Verhoeven et al. is directed by the same principal investigator, Trejla, [sic] who directed the research reported in the Chien et al. reference cited by Examiner to support the rejection under 35 USC §102 and §103 * * * . Applicants do not know what enzyme Verhoeven et al. isolated but do know that Applicants have isolated a very different enzyme.

March 17, 1989, Response to Office Action, Promega Exh 640 at 14-15.

176. Promega argues that the citation to the Verhoven abstract in the March 17, 1989, response to the office action is rendered misleading by the fact that the applicants failed to specify in the March 17, 1989, information disclosure statement that NEB had produced its Taq using a modification of the Chien et al. procedure. The court finds no connection here. As noted above, the failure to report that NEB had used a modified Chien et al. procedure to produce full-length Taq was not misleading. Nor was it rendered misleading by the citation to Verhoven.

177. Promega also argues that an experiment conducted by Stoffel purified full-length Taq polymerase by using the first five steps of the method taught in Kaledin et al., as confirmed by a Western Blot analysis by Lawyer.

178. Promega's evidence, however, does not establish that Stoffel's procedures were identical to those of Kaledin et al., but rather that the procedures were a "slight modification" of Kaledin et al., which is consistent with the inventors' representation in Example I of the '818 patent. See '818 Patent, Promega Exh 654 at col 28:61-62.

179. Accordingly, failure to disclose the results of the experiments identified by Promega was not misleading.

180. The applicants represented to the PTO that Example VI was their best mode. See '818 Patent, Promega Exh 54 at col 28:66-68.

181. Promega claims that the inventors intentionally concealed a better mode for purification of Taq that was known to them before they filed the continuation-in-part application on June 17, 1987.

182. Promega has not shown by clear and convincing evidence that the inventors subjectively believed that they had

developed a better method for the purification of Taq than the method disclosed by Example VI.

183. The inventors claimed during the course of prosecution of the ‘818 patent that they had isolated a different polymerase than the prior art.

184. Promega asserts that this statement itself was materially misleading and made with the intent to deceive the PTO.

185. As noted above, the applicants made several material, misleading statements in the attempt to persuade the examiner that the enzyme they isolated was different from the enzymes isolated by the prior art. Notwithstanding the inventors’ intentionally misleading statements with respect to certain characteristics of their enzyme, or their failure to disclose material information casting doubt on their representations to the PTO, the court cannot find on the present record that the inventors did not actually believe that the enzyme they had isolated was different from the enzyme isolated by the prior art.

186. Nor is the court prepared to find, on the present record, that the enzyme isolated by the inventors was not, in fact, different from that isolated by the prior art. Absent that finding, the court cannot find that the inventors’ claims

that they isolated a different polymerase were of themselves misleading or made with the intent to deceive the PTO.

CONCLUSIONS OF LAW

1. The court has jurisdiction over this action based on 28 USC sections 1331 and 1338.

2. The United States Supreme Court has held that attorneys, agents, and applicants "who have applications pending with the Patent Office or who are parties to Patent Office proceedings have an uncompromising duty to report to it all facts concerning possible fraud or inequitableness underlying the applications in issue." Precision Co v Automotive Co, 324 US 806, 818 (1945). Patent applicants have a duty to prosecute the patent application with candor, good faith and honesty. See Molins PLC v Textron, Inc., 48 F3d 1172, 1178 (Fed Cir 1995).

3. The duty of candor and good faith to the PTO is embodied in 37 CFR section 1.56(a). As promulgated in 1977, Rule 1.56 imposes a duty of candor and good faith toward the PTO on the inventors, on each attorney who prepared or prosecuted the application and on every other person "substantively involved" in the prosecution of the application. See 37 CFR § 1.56(a). This rule in essence codified existing case law and PTO practice. See Fox Industries v Structural Preservation Systems, 922 F2d 801, 804 (1991).

4. The duty of candor extends throughout the patent's entire prosecution history. See Fox, 992 F2d at 803.

5. "Inequitable conduct includes affirmative misrepresentations of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive [the PTO]." Baxter Intern. Inc. v McGaw, Inc., 149 F3d 1321, 1327 (Fed Cir 1998), citing Nobelpharma AB v Implant Innovations, Inc., 141 F3d 1059, 1068-71 (Fed Cir 1998) and Molins, 48 F3d at 1178.

6. A determination of inequitable conduct requires a two-step analysis: first, the trial court must determine whether the withheld or misrepresented information meets a threshold level of materiality; second, the trial court must determine whether the evidence shows a threshold level of intent to mislead the PTO. See Baxter, 149 F3d at 1327, citing Halliburton Co. v Schlumberger Technology Corp., 925 F2d 1435, 1439 (Fed Cir 1991).

7. "Once threshold findings of materiality and intent are established, the court must weigh them to determine whether the equities warrant a conclusion that inequitable conduct occurred." Molins, 48 F3d at 1178.

8. "[M]ateriality does not presume intent, which is a separate and essential component of inequitable conduct." Manville Sales Corp. v Paramount Systems, Inc., 917 F2d 544, 552

(Fed Cir 1990), quoting Allen Organ Co v Kimball Intern., Inc, 839 F2d 1556, 1567 (Fed Cir 1988).

9. The court must balance materiality and intent: "[t]he more material the omission, the less culpable the intent required, and vice versa." Halliburton, 925 F2d at 1439.

10. The determination of inequitable conduct is within the discretion of the trial court. See id at 1439-40.

11. Under 35 USC section 282, a patent is presumed valid; inequitable conduct therefore requires proof by clear and convincing evidence. See Manville, 917 F2d at 551; American Hoist & Derrick Co. v Sowa & Sons, 725 F2d 1350, 1360 (Fed Cir 1984).

12. The "clear and convincing" standard of proof of facts is an intermediate standard which lies somewhere between "beyond a reasonable doubt" and a "preponderance of the evidence." Addington v Texas, 441 US 418, 425 (1979).

13. Clear and convincing evidence requires proof that a contention is "highly probable." Colorado v New Mexico, 467 US 310, 316 (1984); Buildex, Inc. v Kason Indus., Inc., 849 F2d 1461, 1463 (Fed Cir 1988).

14. "The duty of candor before the PTO has been codified in 37 CFR § 1.56. At the time of the prosecution of the '818 patent this section defined information as 'material' when 'there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent.' The Federal Circuit has adopted this definition as the threshold standard of materiality." August 9, 1996, Order at 42, citing LaBounty Mfg, Inc v United States Intern. Trade Com'n, 958 F2d 1066 (Fed Cir 1992).

15. "Close cases [of materiality] should be resolved by disclosure, not unilaterally by the applicant." LaBounty, 958 F2d at 1076.

16. "It is not inequitable conduct to omit telling the patent examiner information that the applicant in good faith believes is not material to patentability." Allied Colloids Inc. v American Cyanamid Co., 64 F3d 1570, 1578 (Fed Cir 1995); see also Symbol Technologies, Inc. v Opticon, Inc., 935 F2d 1569, 1582 (Fed Cir 1991); Stevenson v Intern. Trade Com'n, 612 F2d 546, 554-55 (CCPA 1979).

17. A patent applicant, however, cannot "cultivate ignorance, or disregard numerous warnings that material information or prior art may exist, merely to avoid actual

knowledge of that information or prior art." FMC Corp. v Hennessy Industries, Inc., 836 F2d 521, 526 n.6 (Fed Cir 1987)

18. "Because disclosure of the best mode is statutorily required, see 35 USC § 112, failure to disclose the best mode is inherently material and, we believe, reaches the minimum level of materiality necessary for a finding of inequitable conduct." Consolidated Aluminum Corp. v Foseco Intern. Ltd, 910 F2d 804, 808 (Fed Cir 1990). Omission of the best mode, however, only constitutes inequitable conduct if the best mode was intentionally concealed. See id.

19. In Amgen, Inc v Chugai Pharmaceutical Co, Ltd, 927 F2d 1200, 1210 (Fed Cir 1991), the Federal Circuit determined, as a matter of first impression, whether applicants for patents involving "novel genetically-engineered subject matter" must deposit samples of the organism in a public depository in order to satisfy the best mode requirement. The court concluded that: "If the cells can be prepared without undue experimentation from known materials, based on the description in the patent specification, a deposit is not required." Id at 1211; see also 37 CFR § 1.802.

20. "Information may be material even if its disclosure does not render the claim unpatentable * * * ." August 9, 1996, Order at 43, citing Molins, 48 F3d at 1179-80. "To be material, a misrepresentation need not be relied on by

the examiner in deciding to allow the patent. The matter misrepresented need only be within a reasonable examiner's realm of consideration." Merck & Co., Inc. v Danbury Pharmacal, Inc., 873 F2d 1418, 1421 (Fed Cir 1989).

21. Courts have declined to find inequitable conduct based on alleged micharacterizations of references supplied to an examiner because PTO examiners are free to reach their own conclusions regarding the prior art and should not thoughtlessly accept an applicant's interpretation. See Gambro Lundia AB v Baxter Healthcare Corp., 110 F3d 1573, 1581 (Fed Cir 1997); Akzo N.V. v US Intern. Trade Com'n, 808 F2d 1471, 1482 (Fed Cir 1986).

22. "To satisfy the intent to deceive element of inequitable conduct, 'the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive.'" Paragon Podiatry Laboratory, Inc. v KLM Laboratories, Inc., 984 F2d 1182, 1189 (Fed Cir 1993), quoting Kingsdown Medical Consultants v Hollister, Inc, 863 F2d 867, 876 (Fed Cir 1988).

23. "Intent to deceive the PTO need not be proven by direct evidence; indeed, 'it is most often proven by a showing of acts, the most natural consequence of which are presumably intended by the actor.'" August 9, 1996, Order at 43, quoting

Molins, 48 F3d at 1180, quoting Kansas Jack, Inc v Kuhn, 719 F3d 1144, 1151 (Fed Cir 1983).

24. The requirement of proving intent to deceive the PTO is satisfied by a showing of recklessness. See Modine Mfg. Co. v Allen Group, Inc., 14 USPQ2d 1210, 1215 (ND Cal 1989), aff'd, 917 F2d 538 (Fed Cir 1990).

25. "[A] finding that particular conduct amounts to 'gross negligence' does not itself justify an inference of intent to deceive; the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." Kingsdown, 863 F2d at 876.

26. "[G]rossly negligent conduct may or may not compel an inference of an intent to mislead. Such an inference depends upon the totality of the circumstances, including the nature and level of culpability of the conduct and the absence or presence of affirmative evidence of good faith." Hewlett-Packard Co. v Bausch & Lomb Inc, 882 F2d 1556, 1562 (Fed Cir 1989).

27. "Intent may be inferred where a patent applicant knew, or should have known, that withheld information would be material to the PTO's consideration of the patent application." Critikon, Inc v Becton Dickinson Vascular Access, Inc., 120 F3d 1253, 1256 (Fed Cir 1997); see also La Bounty, 958 F2d at 1076.

28. In the absence of a good faith explanation, an intent to mislead the PTO may be inferred from a pattern of nondisclosure. See Critikon, Inc, 120 F3d at 1259; Paragon Podiatry, 984 F2d at 1193.

29. The 1985 edition of the Manual of Patent Examining Procedure (MPEP) provides that:

> Simulated or predicted test results and prophetical examples (paper examples) are permitted in patent applications. Working examples correspond to work actually performed and may describe tests which have actually been conducted and results that were achieved. Paper examples describe the manner and process of making an embodiment of the invention which has not actually been conducted. Paper examples should not be represented as work actually done. No results should be represented as actual results unless they have actually been achieved. Paper examples should not be described using the past tense.

Patent and Trademark Office, United States Department of Commerce, Manual of Patent Examining Procedure at 600-36 (United States Government Printing Office, Fifth Edition, Revision 2, 1985).

30. The 1985 edition of MPEP also provides that:

> Care should be taken to see that inaccurate statements or inaccurate experiments are not introduced into the specification, either inadvertently or intentionally. For example, stating that an experiment "was run" or "was conducted" when in fact the experiment was not run or conducted in a misrepresentation of the facts. No results should be represented as actual results unless they have actually been achieved. Paper examples should not be described using the past tense.

> Also, misrepresentations can occur when experiments which were run or conducted are inaccurately reported in the specification, e.g., an experiment is changed by leaving out one or more ingredients.

Id at 2000-9 (citations omitted).

31. The MPEP commonly is relied upon as a guide to patent attorneys and patent examiners on procedural matters. The MPEP has no binding force, but is entitled to notice as an official interpretation of statutes or regulations with which it is not in conflict. See Litton Systems, Inc v Whirlpool Corp, 728 F2d 1423, 1439 (Fed Cir 1984), overruled on other grounds by Two Pesos, Inc v Taco Cabana, Inc, 505 US 763 (1992); accord Molins, 48 F3d at 1180 n10.

32. The fact that an applicant fails to indicate to the examiner that an example is prophetic does not automatically establish the materiality of the example or the representations contained therein. The party asserting inequitable conduct must still establish that the misrepresentation regarding whether the example had actually been performed was material and made with an intent to deceive the PTO. See Atlas Powder Co. v E.I. Dupont De Nemours, 750 F2d 1569, 1578 (Fed Cir 1984).

33. Failure of an applicant to follow the guidelines in the MPEP is not, in and of itself, inequitable conduct. See Nintendo of America Inc. v Magnavox Co., 707 F Supp 717, 730 (SDNY 1989).

34. A finding of inequitable conduct renders the entire patent unenforceable. See J.P. Stevens & Co., Inc. v Lex Tex Ltd., 747 F2d 1553, 1561 (Fed Cir 1984), overruled on other grounds by Kingsdown, 863 F2d 867.

35. The findings of fact and conclusions of law recited above demonstrate that the '818 patent was procured by inequitable conduct. Specifically, Promega has demonstrated by clear and convincing evidence that the applicants committed inequitable conduct by:

(1) withholding material information in their possession that Taq does not bind, or binds only weakly, to phosphocellulose columns;

(2) making misleading statements regarding the relative fidelity of Taq as compared to the prior art enzymes;

(3) claiming that Taq purified by the method taught in Example VI had a specific activity of -250,000 units/mg;

(4) presenting Example VI as though it had been performed when, in fact, it had not been performed;

(5) making deceptive, scientifically unwarranted comparisons between the specific activity of the claimed enzyme and the specific activity reported by Chien et al. and Kaledin et al.;

(6) withholding information in applicants' possession that Taq interacts with matrices used in size exclusion chromatography;

(7) claiming that Taq purified according to the method taught in Example VI yielded a single -88 kd band on an SDS PAGE mini-gel and

(8) claiming that the Taq produced was free from nuclease contamination.

Each of the foregoing misstatements and each item of information withheld was material to the prosecution of the application that led to issuance of the '818 patent. Each of the foregoing misstatements or omissions was made with an intent to mislead the PTO or with such recklessness as to afford no inference other than that they were made with an intent to deceive.

36. All claims of the '818 patent are therefore unenforceable. The parties shall appear for a case management conference on January 27, 2000, at 3:30 p.m.

IT IS SO ORDERED.

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VAUGHN R. WALKER
United States District Judge